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INSULIN RESISTANCE AND SENSITIVITY

By the present generation Sidney Ringer is chiefly remembered as the inventor of the fluid known by his name. Yet we owe him two other debts: at a time when treatment was only cursorily mentioned in textbooks of medicine he produced an admirable work on therapeutics; and he was a leader in the struggle, against strenuous opposition, for the right of Londoners to listen to good orchestral music on Sundays. Since amid all the demands of clinical work Ringer continued his physiological researches it is fitting that Professor H. P. Himsworth should have commemorated him in a lecture based on both laboratory experiment and clinical observation concerning the vexed question of insulin resistance and sensitivity. Apart from a temporary resistance to insulin resulting from intercurrent infections, and apparent resistance due to dietetic irregularities, perhaps concealed from the medical attendant, there remains a group of a more persistent type. Rarely, however, can this attain the level described by H. J. Wiener,[1] in which a Jewish patient aged 58 required 3,250 units of insulin in twenty-four hours to extricate him from coma, and a routine daily dose of 440 units to maintain health.

It has been recognized for some years that alterations in the diet of normal individuals affect the blood-sugar curve, and that in general an increased carbohydrate diet increases tolerance to carbohydrate. This is difficult to reconcile with the idea of carbohydrate excess as an important aetiological factor in diabetes, but is not the point with which Professor Himsworth is concerned. Noting that a low-carbohydrate–high-fat diet renders the subject more resistant to insulin than a high-carbohydrate–low-fat one, he began to wonder whether there may be a type of diabetes due not to lack of insulin but to insensitivity to it. How otherwise are we to account for fatal cases of diabetes in which the islets of Langerhans are found to be normal? He therefore designed a method, of which the details will be found in his lecture, for testing this hypothesis. This enabled him to differentiate between cases in which intravenous insulin promptly suppressed the rise of blood sugar after taking 50 grammes of glucose and those in which it did not. On the whole the members of the former group are younger and thinner and have a normal blood pressure and healthy arteries; their disease has a rapid onset, ketosis is the rule, and insulin easily induces hypoglycaemic reactions. The latter group has precisely opposite characteristics. The abnormality of the insulin–glucose curves is corrected by insulin in the former or insulin-sensitive group, but not at all in the latter or insulin-insensitive. This suggests inefficient rather than deficient insulin action as a cause of such insensitivity, since giving more insulin does not affect the position.[2]

The most characteristic action of insulin is its ability to increase the rate at which the peripheral tissues remove sugar from the blood, a rough idea of which can be obtained by comparing the sugar content in the capillaries with that in the veins after an injection of insulin. The action of insulin in accelerating the rate at which the peripheral tissues remove sugar from the blood is normal in the insulin-sensitive; in the insulin-insensitive it is impaired. In the latter group the condition of the peripheral tissues evidently renders them unable to abstract sugar from the blood at the normal rate, even in the presence of normal pancreatic secretion, so that an overflow into the urine results. This applies mainly to the first hour after insulin; in the long run the total effect of insulin tends to approximate in the two types of cases. Insulin resistance therefore results from retardation of insulin action rather than from its neutralization or destruction. Several observers—R. D. Lawrence, T. H. Oliver, A. Marble, and others—have suggested that this inhibitory action may be, at all events in part, due to the pituitary; now we have some evidence that this is so. Naturally the important work of F. G. Young comes to mind, for he showed that permanent diabetes could be produced in dogs by a course of injections of crude anterior pituitary extracts; but these animals were diabetics of the insulin-sensitive type with changes in the islets of Langerhans. Now if the pituitary be removed from a normal animal the usual changes in insulin-sensitivity which follow variations in dietary carbohydrate do not occur, though they can be imitated by appropriate amounts of pituitary extract. This suggests that the substance which induces resistance to insulin is secreted by the pituitary, and it is noteworthy that the diabetes of Cushing's syndrome and acromegaly is of the insulin-resistant type. Moreover, irradiation of the pituitary region ameliorates the diabetes and increases insulin-sensitivity. Although no trace of an anti-insulin pituitary factor has been found in the blood or urine of ordinary diabetics, whether of the sensitive or usual insensitive type, definite amounts have been found in the urine of a case of acromegaly and two cases of Cushing's syndrome, and, further, this amount was diminished by irradiation. We may therefore state that while the anterior pituitary is responsible for the diabetes associated with hyperpituitarism, its responsibility as a primary factor in ordinary cases of human diabetes at present rests purely on analogy. An important advance has, however, been achieved by distinguishing between diabetes due to deficiency of the pancreatic internal secretion and that due to some mechanism acting peripherally. It is an additional point of great interest to learn that the shifting of the sugar curve in answer to changing diets is at any rate effected through the pituitary, which thus appears to be charged with yet another regulating function. This is presumably related to its power of exciting the liver to convert protein and probably even fat into sugar when carbohydrate intake is restricted.[3]

[1] *Amer. J. med. Sci.*, 1938, **196**, 211.

[2] *Clin. Sci.*, 1939, **4**, 119, 153.

[3] *British Medical Journal*, 1940, **1**, 351.